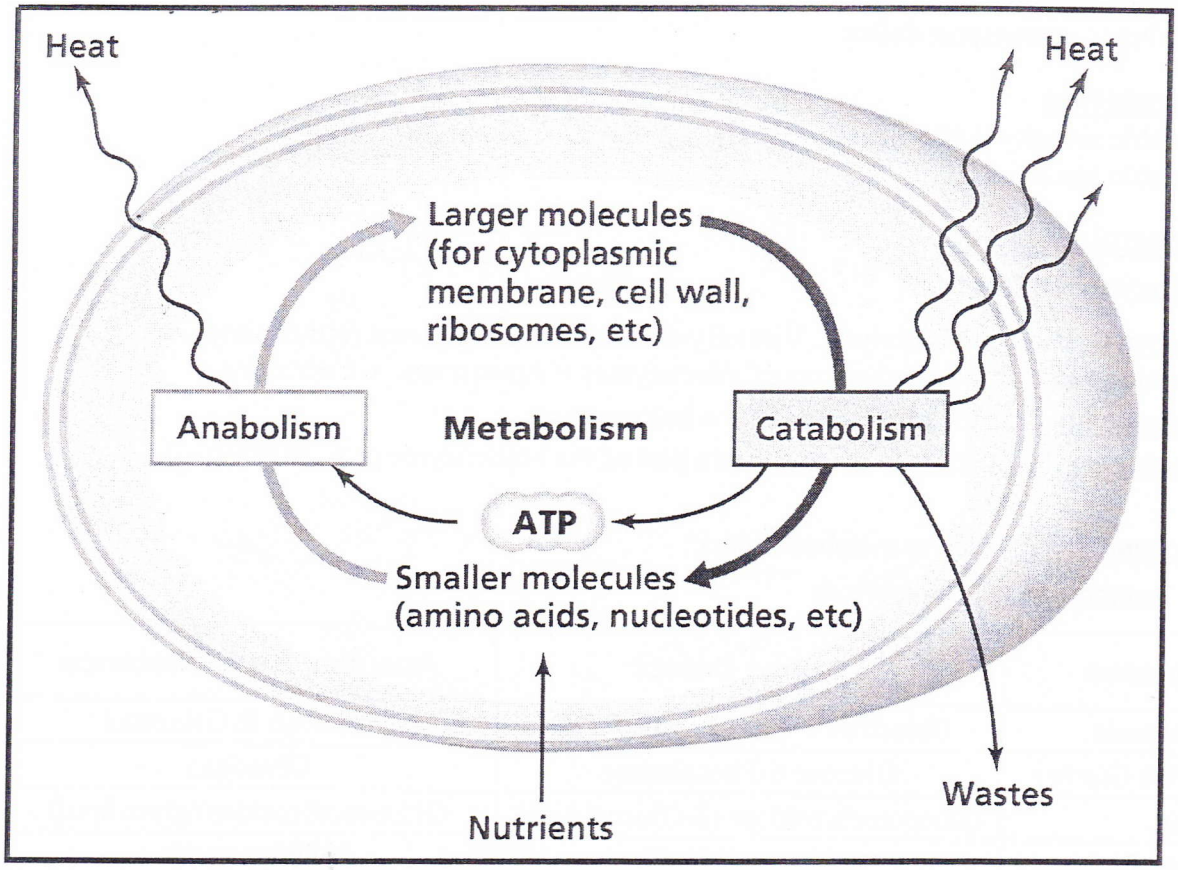

Inborn Errors of Metabolism

(For Master degree)

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Inborn Errors of Metabolism

Definition

- Group of inherited biochemical disorders caused by enzyme, coenzyme, receptor, membrane or transport defect

Presentation

- Variable severity [Mild-Severe-Lethal]
- Variable age of onset

Biochemical Defect

A) Enzyme Defects

Enzymes: Biological catalysts. Virtually all enzymes are proteins (either simple or conjugated). Conjugated enzyme (holoenzyme) = Apoenzyme + Coenzyme

Apoenzyme: It is the protein part of the holoenzyme

Coenzyme: It is the organic non-protein part of the holoenzyme (e.g., vitamin…)

Enzyme defect leads to metabolic block:

a. Accumulation of precursors

Disease		Enzyme Defect	Accumulated substance
Galactosemia		Galactose 1-P-uridyltransferase	Galactose & Galactitol
GSD *(Von Gierke)*		Glucose 6-Phosphatase	Glycogen
Gaucher		Glucocerebrosidase (β-Glucosidase)	Glucocerebrosides (glycolipid)
Niemann-Pick		Sphingomyelinase	Sphingomyeline
MPS *(Hurler)*		α-L- Iduronidase	GAG = Glycosaminoglycan
GM_1 Gangliosidosis		β-Galactosidase	Gangliosides
GM_2	**Tay-Sachs**	Hexosaminidase A	Gangliosides
	Sandhoff	Hexosaminidase A & B	Gangliosides

b. Deficiency of end-product

Albinism: (↓↓ Melanin) Tyrosine —*Tyrosinase*→ Melanin

c. Opening of alternative pathway

Normally: Phenylalanine —*P.hydroxylase*→ Tyrosine

Phenylketonuria: ↑↑ Phenylalanine → ↑↑ Phenylpyruvate, lactate& acetate

B) Transport across cell membranes

a. Transport across cell membrane

Specific vitamin B_{12} malabsorption due defective receptors for IF-B_{12} complex

b. Transport across lysosomal membrane

Cystinosis: Trapping of cystine inside the lysosomes. [Action of Cysteamine??]

C) Binding Proteins

a. Hemoglobin carries O_2: HbM cannot carry O_2

b. Ceruloplasmin carries Copper: Wilson disease

When to suspect (= Clinical Picture)

1. **Neonatal Presentation:** Poor feeding, lethargy, vomiting, seizures [DD: **Sepsis**, ↓↓Ca, ↓↓G]
2. **Consanguineous parents & positive family history**
3. **Unexplained MR, coma, convulsions or developmental delay**
4. **Unexplained vomiting, acidosis**
5. **Unexplained organomegaly (Hepatomagaly)**
6. **Unexplained odor:**
   - ☒ **PKU:** Mousy or musty
   - ☒ **Tyrosinemia (& Hypermethioninemia):** Boiled cabbage
   - ☒ **Maple syrup urine:** Maple syrup
   - ☒ **Isovaleric acidemia:** Sweaty foot
   - ☒ **Multiple carboxylase deficiency:** Tomcat urine
7. **Unexplained muscle weakness or cardiomyopathy**
8. **Unexplained renal stones**
9. **Episodic pattern** (with disease-free intervals)

Neonatal screening (American College of Medical Genetics = ACMG)

	Primary Disorders	Secondary Disorders
Organic acid	▪ Methylmalonic acidemia ▪ Propionic acidemia ▪ Isovaleric acidemia ▪ Glutaric aciduria type I ▪ Multiple carboxylase deficiency ▪ Beta-ketothiolase deficiency	▪ Malonic acidemia
Fatty acids	▪ MCAD, VLCAD, LCHAD ▪ Carnitine uptake defect	▪ Carnitine palmitoyl transferase I deficiency ▪ Carnitine palmitoyl transferase II deficiency
Amino acids	▪ Phenylketonuria ▪ Maple syrup urine disease ▪ Homocystinuria ▪ Citrullinemia ▪ Argininosuccinic acidemia ▪ Tyrosinemia (type I)	▪ Tyrosinemia type II ▪ Tyrosinemia type III
Hemoglobin	▪ Sickle cell anemia ▪ Hemoglobin S-β-thalassemia ▪ Hemoglobin SC disease	▪ Hemoglobin variant (Hemoglobin E)
Others	▪ Congenital hypothyroidism ▪ Biotinidase deficiency ▪ Congenital adrenal hyperplasia ▪ Galactosemia ▪ Hearing deficiency ▪ Cystic fibrosis	▪ Galactose epimerase deficiency ▪ Galactokinase deficiency

Treatment of Genetic Diseases

1. Enzyme Induction
Phenobarbitone in Crigler-Najjar syndrome type II (AD)

2. Enzyme Replacement

- ☒ Gaucher disease
- ☒ Pompe disease (GSD type II)
- ☒ Fabry disease
- ☒ ADA deficiency
- ☒ Some MPS
- ☒ Cystic fibrosis

3. Recombinant proteins

- ☒ GH
- ☒ Insulin
- ☒ Factor VIII
- ☒ EPO
- ☒ GM-CSF
- ☒ Interferon

4. Replacement of Hormones

- ☒ Hydrocortisone (CAH)
- ☒ 9-α fludrocortisol (CAH)
- ☒ GH (Hypopituitarism)
- ☒ Thyroxine (Congenital hypothyroidism)

5. Replacement of vitamins

- ☒ B_1 (Maple syrup urine disease)
- ☒ B_6 (Homocystinuria)
- ☒ B_{12} (Methylmalonic acidemia)
- ☒ Biotin (Propionic acidemia)
- ☒ Folic acid (Megaloblastic anemia)
- ☒ Vitamin D (Vitamin D resistant rickets)

6. Dietary restriction

- ☒ Maple syrup urine (V I L)
- ☒ Methionine (Homocystinuria)
- ☒ PKU (Phenylalanine)
- ☒ Urea cycle disease (proteins)
- ☒ Galactosemia (galactose, Lactose)
- ☒ Hypercholesterolemia (Lipids)

7. Induction of alternative pathways
Na benzoate in urea cycle defects (to eliminate NH_3)

8. Preventive therapy
Avoidance of certain drugs in G6PD deficiency

9. BM or liver transplantation

10. Portocaval anastomosis
In cases of portal hypertension (GSD type IV)

11. Extracorporeal therapy
Plasmapheresis in the Rx of hypercholesterolemia

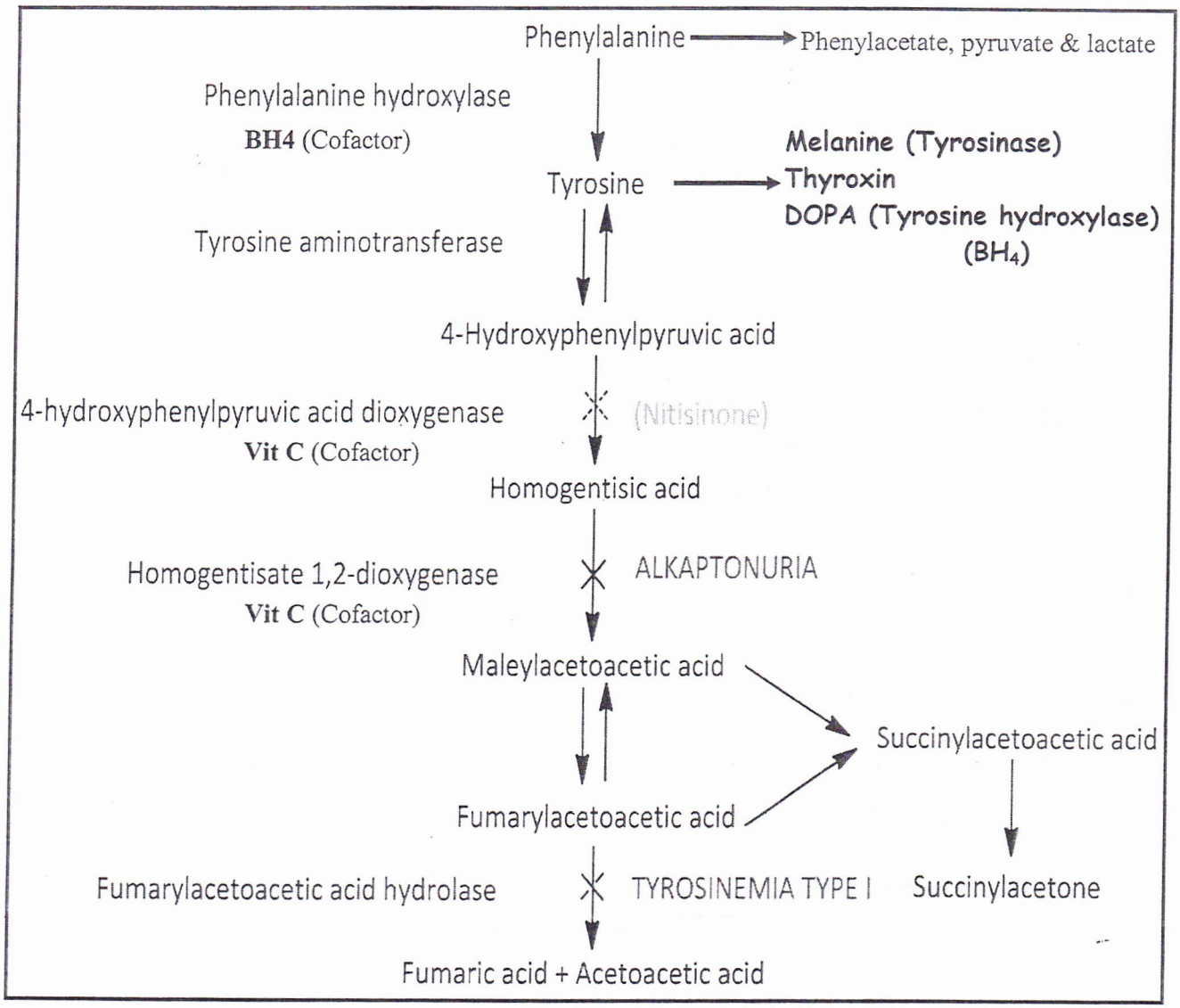
12. Gene therapy *(Give examples)*

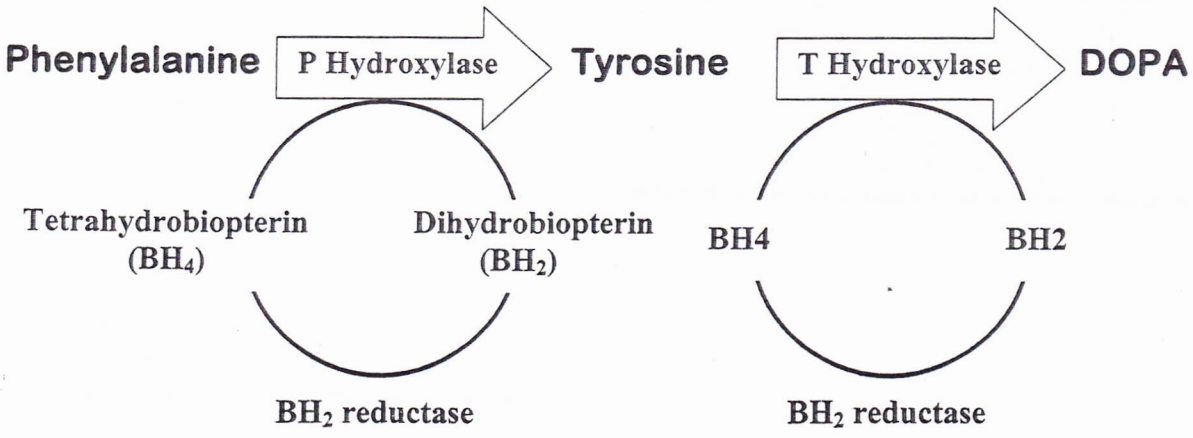
Note

Essential Amino acids	Non-essential Amino acids
▪ Phenyalanine	▪ Tyrosine
▪ Valine, leucine, isoleucine	▪ Glycine glutamic, glutamine
▪ Threonine, methionine	▪ Alanine, proline
▪ Arginine, lysine, histidine	▪ Cysteine, serine
▪ Tryptophan	▪ Aspartic, asparagine

Disorders of Protein Metabolism

Phenylalanine & Tyrosine





Phenylketonuria

Definition

- **AR** (12q for PAH)
- **Classic PKU:** Plasma phenylalanine level > 20 mg/dL
- **Non-PKU hyperphenylalaninemia:** Plasma phenylalanine level < 20 mg/dL [but > 2 mg/dL]

Biochemical Defect

- ↓↓ Phenylalanine hydroxylase ⟶ ↑↑ Phenylalanine ⟶ CNS damage (mechanism?)

Epidemiology

- **Non-PKU hyperphenylalaninemia:** 1:50.000 live births
- More common in whites

Clinical Picture (Classic PKU)

- Normal at birth
- CNS: Seizures (25%), spasticity, tremors, microcephaly, MR *"Normal mentality in 2-5%"*
- Skin: Light complexion *(Blond, blue eyes)*, seborrheic rash, eczema
- Vomiting

Investigations

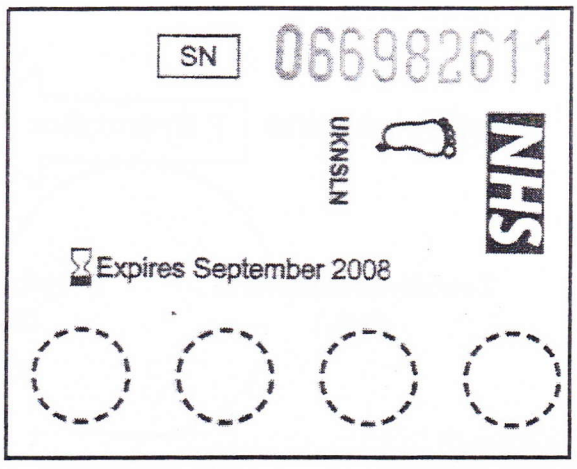
- Neonatal screening
  - Past: Bacterial inhibition test of Guthrie
  - Now: TMS
  - Time: In the 1st 48 hrs after protein intake is recommended
- Plasma phenylalanine
- EEG: Abnormalities in > 50%
- MRI & MRS: ↑↑ Phenylalanine
- Prenatal diagnosis is available (CVS)

Treatment

- Phenylalanine restricted diet for **life**
  - Target level: 2-6 mg/dL
  - Phenylalanine deficiency: Lethargy, FTT, anemia, anorexia, diarrhea
  - Tyrosine becomes essential
- Oral BH_4 (10 mg/Kg/day): ↓↓ Phenylalanine level in 50% of cases

Maternal PKU

Mechanism: Phenylalanine is teratogenic
C/P: Microcephaly, MR, CHD
Prevention: Phenylalanine-restricted diet (Phe level should be < 6 mg/dL)



Hyperphenylalaninemia due to BH_4 deficiency

Biochemical Defect

- **BH4** is a cofactor for PAH, Tyrosine hydroxylase, Tryptophan hydroxylase & NO^-synthase
- So, important in synthesis of dopamine & serotonine **[Neurotransmitters]**

Epidemiology

- 1-3% of infants with hyperphenylalaninemia are due to defect in BH_4 metabolism

Clinical Picture

- Extrapyramidal: Choreoathetosis, dytonia, hypotonia (Diurnal variation)
- Seizures, MR
- Hyperprolactinemia (why?)

Investigations

- Neonatal screening & plasma phenylalanine: Hyperphenylalaninemia
- BH_4 loading test: ↓↓ plasma phenylalanine level
- ↓↓ CSF dopamine & serotonin
- Urinary biopterin
- Enzyme assay?? (Blood & liver)

Treatment

- Phenylalanine restricted diet
- Oral BH_4
- Neurotransmitters precursors: Dopa & tryptophan [Carbidopa should be given, why?]

BH_4 deficiency without Hyperphenylalaninemia
(= AD Dopa-responsive dystonia = Segawa syndrome)

Biochemical Defect ↓↓ **BH4** occurs due to GTP cyclohydrolase deficiency **(AD form)**

Clinical Picture Extrapyramidal: Dytonia starting in the LL (Diurnal variation)

Investigations

- **No** Hyperphenylalaninemia,
- ↓↓ CSF dopamine
- Enzyme assay & gene analysis

Treatment Dopa [Carbidopa should be given]

Tyrosinemia type I

Definition

- **AR**
- Severe disease affecting liver, kidney & peripheral nerves

Biochemical Defect

- ↓↓ Fumarylacetoacetate hydrolase ⟶ ↑↑ Succinylacetone ⟶ Organ damage

Epidemiology

- 1:1000.000 live births (More common in those with French & Scandinavian ancestry)

Clinical Picture (**Onset** = 2-6 months of age)

A. Hepatic affection

- Fever, irritability, vomiting, hepatomegaly, jaundice, hypoglycemia, coagulopathy
- Boiled cabbage oder *(↑↑ Methionine, why?)*
- Liver cell failure, cirrhosis, hepatocellular carcinoma (> 2 yrs)

B. Renal affection

- Proximal RTA
- Vitamin D-resistant rickets

C. Peripheral neuropathy

- Pain, hypertonia, paralysis

Investigations

- ↑↑ Blood & urine succinylacetone
- ↑↑ α-Fetoprotein (**Marked**)
- Investigation of liver, hematologic & renal affection: ALT, AST, bilirubin, glucose, CBC
- Plasma tyrosine level??
- Neonatal screening (succinylacetone)
- Prenatal diagnosis is available (AF succinylacetone or CVS)

Treatment

- Phenylalanine & tyrosine restricted diet
- Nitisinone (NTBC):
  - Originally developed as a herbicide
  - Mechanism:
  - 2-Nitro-4-trifluoromethylbenzoyl-1,3-cyclohexanedione
  - Tyrosine corneal crystals may develop
- Liver transplantation

Orfadin®
nitisinone

	Tyrosinemia II (Oculocutaneous)	Tyrosinemia III
Defect	↓↓ Tyrosine aminotransferase	↓↓ Hydroxyphenylpyruvate dioxygenase
Genetics	AR (16q)	AR (12q)
C/P	▪ **Skin:** Palmar & plantar keratosis ▪ **Ocular:** Pain, redness, ↑↑ tears, ulcer ▪ **MR:** Mild	▪ Seizures, MR, ataxia ▪ Self mutilation
Diagnosis	▪ ↑↑ Plasma tyrosine	▪ ↑↑ Plasma tyrosine ▪ ↑↑ urine HPP
TTT	▪ Phenylalanine & tyrosine restricted diet	▪ Diet + Vitamin C

Alkaptonuria

Definition
- **AR** (3q), rare (1:250.000)

Biochemical Defect
- ↓↓ Homogentisic acid dioxygenase ⟶ ↑↑ Homogentisic acid ⟶ Tissue accumulation

Clinical Picture
- The only sign of alcaptonuria in children is **"black urine on standing"**
- Ochronosis: Darkening of tissues (sclera & ear)
- Arthritis (big joints): Adult

Investigations
- ↑↑ Urine homogentisic acid

Treatment
- Phenylalanine & tyrosine restricted diet
- Nitisinone (NTBC)
- Vitamin C

Transient Tyrosinemia of the Newborn

Definition
- ↑↑ Tyrosine level in premature neonates (receiving ↑↑ protein diet)

Biochemical Defect Immature HPPD ⟶ ↑↑ Tyrosine level

Clinical Picture Lethargy, poor feeding, screening tests

Investigations ↑↑ Plasma tyrosine & ↑↑ urine hydroxyphenylpyruvic acid

Treatment Dietary protein restriction & Vitamin C

Tyrosine Hydroxylase Deficiency

(= AR Dopa-responsive dystonia = Infatile Parkinsonism)

Definition
- **AR** disease due to DOPA deficiency

Biochemical Defect
- Tyrosine hydroxylase deficieny
- Tyrosine ⟶ DOPA

Clinical Picture (as Segawa syndrome)
- Extrapyramidal: Dytonia, hypertonia, oculogyric crises, infantile parkinsonism
- No diurnal variation

Investigations
- ↓↓ CSF dopamine

Treatment
- Dopa [Carbidopa should be given]

Albinism

Definitions

- **Albinism:** Complete or partial absence of melanin pigment in the skin, hair & eyes
- **Melanocyte:** are melanin-producing cells located in skin (epidermis), eye & inner ear
- **Melanosome:** Organelle containing melanin
- **Melanin:** is a dark pigment present in skin, eye & hair (absorb UV rays)
- **Optical system development** is highly dependent on the presence of melanin

Biochemical Defect

- Tyrosine ⟶ Melanin
- Types of melanin: **Pheomelanin** (yellow-red) & **Eumelanin** (Brown-black)
- Albinism may be Oculocutaneous (generalized), ocular or localized
- Albimism may be complete (No pigment at all) or partial

Clinical Picture

A. Skin affection

- Lack of skin pigment (Fair or white skin)
- ↑↑ Risk of sunburn & skin cancers

B. Visual affection

- Photophobia, ↓↓ visual acuity, red reflex
- Nystagmus, squint, astigmatism, amblyopia "Poor transmission to the brain"
- Optic nerve hypoplasia, foveal hypoplasia
- Abnormal decussation of optic nerve fibres (abnormal VEP)

C. Ear affection

- ↑↑ Susceptibility to ototoxic drugs

Treatment Avoid sun exposure & use of sunscreens (with high SPF)

Oculocutaneous Albinism

	Defect	Manifestations	
OCA1	Tyrosinase deficiency	**OCA1A** (Severe)	▪ Evident at birth & persistent (remains unchanged) ▪ Milky white skin, white hair, red gray eyes ▪ No tan, No pigmented nevi
		OCA1B (Mild)	▪ Evident at birth & improve with age ▪ Light blond skin & light blue eyes ▪ Can develop pigmented nevi & tan
OCA2	Normal Tyrosinase	▪ At birth: Some pigmentation & ↑↑ with age (pigment accumulation) ▪ Yellow hair, red gray eyes ▪ Can develop pigmented nevi (Not tan) ▪ **Pradder-Willi & Angelman** may have some ↓↓ pigments	
OCA3		▪ Reddish hair ▪ Reddish brown skin	
OCA4		▪ Similar to OCA2	
Hermansky-Pudlak		▪ AR (Defect in melanosomes & platelet dense bodies) ▪ OCA, platelet dysfunction (why?)	
Chediak-Higashi		▪ Immunodeficiency, silvery hair, light skin ▪ Defective degranulation (Neutropenia, platelet dysfunction)	

Ocular Albinism

- XLR
- Visual manifestation with **normal** skin pigmentation
- Late-onset sensorineural deafness has been reported

Localized Albinism

A. Piebaldism

- AD condition
- White forelock
- White macules on the face, trunk & extremities

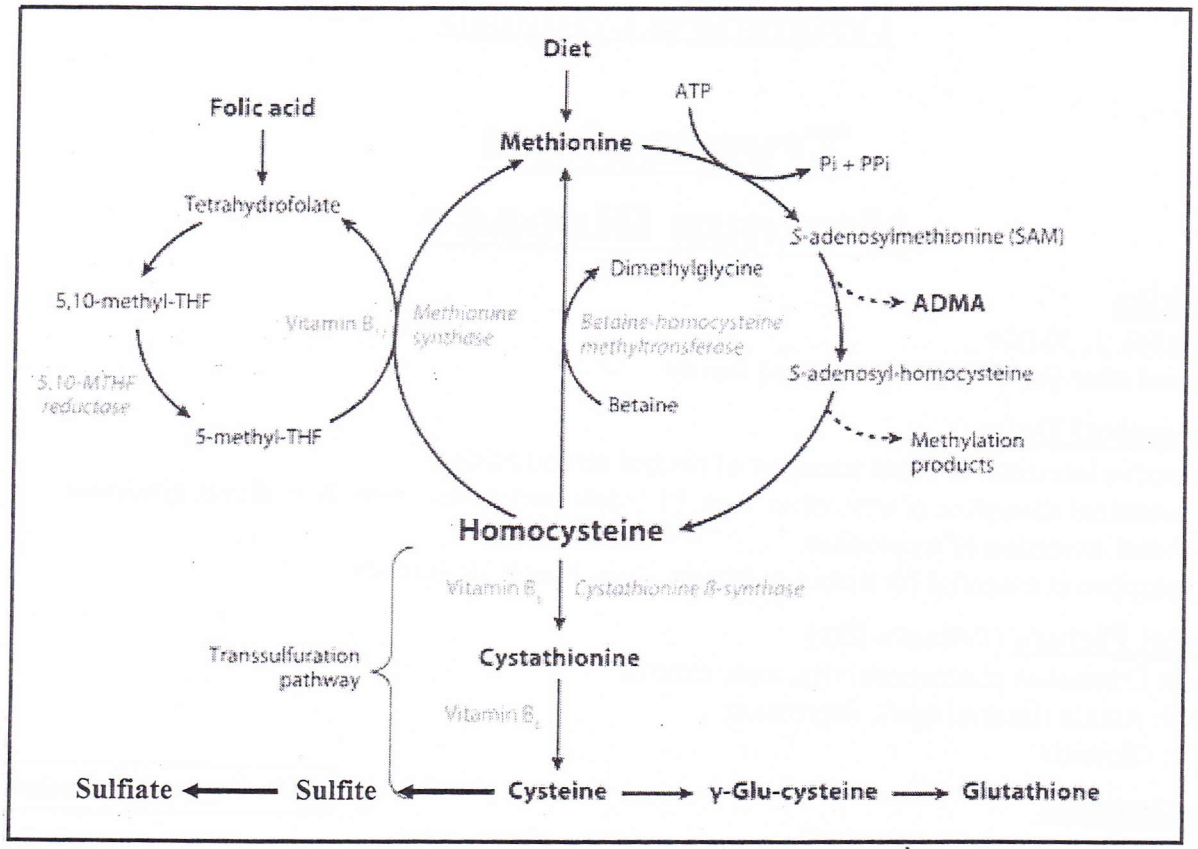
B. Waardenburge syndrome

- AD condition (2q, 3p), 4 types
- White forelock
- Broad nasal bridge, heterochromia, sensorineural deafness,

C. Hypomelanosis of Ito

- Hypopigmentation following Blaschko's lines *(Invisible skin lines)*

Methionine Metabolism



Biochemical Defect

- Methionine is an essential amino acid
- Methionine catabolism: Methyl group donor & cysteine
- Most homocysteine is remethylated to methionine (catalyzed by methionine synthase)

Homocystinuria

	Homocystinuria	Marfan syndrome
Etiology	Cystathionine synthase ↓↓	Defect in collagen fibers
Inheritance	AR	AD
Mentality	MR	Normal
Muculoskeletal	Arachnodactyly (2 Tests), Pectus excavatum, High arched palate, Kyphoscoliosis	The same + Hernias Pneumothorax
Bone density	Osteoporosis	Normal
Joints	Stiff	Lax
Cardiovascular	AR, MR	AR, MR, Aortic dissection
Ocular	Myopia Lens dislocation (Downwards)	Myopia Lens dislocation (Upwards)
Vascular thrombosis	↑↑ risk of thrombosis	No ↑↑ risk of thrombosis
Investigations	↑↑ Homocystine in urine	No ↑↑ Homocystine in urine
Treatment	Low methionine diet B6 & folic acid	Supportive

Cysteine & Cystine Metabolism

Cystinuria & Cystinosis

Tryptophan

Hartnup Disease

Definition

- **AR** (5p), 1: 30.000
- Named after the 1st affected reported family

Biochemical Defect

- Defective intestinal & renal transport of neutral amino acids
- ↓↓ Intestinal absorption of tryptophan ⟶ ↑↑ Indole derivatives ⟶ **Blue diaper syndrome**
- ↑↑ Renal excretion of tryptophan
- Tryptophan is essential for niacin synthesis ⟶ Niacin deficiency

Clinical Picture (Pellagra-like)

- Skin: Cutaneous photosensitivity, rash, eczema
- CNS: Ataxia (intermittent), depression
- GIT: Glossitis

Investigations

DD: Fanconi syndrome

- Neonatal screening
- ↑↑ Urine **neutral** amino acids (Tryptophan, phenylalanine, tyrosine, alanine…)

Treatment

Nicotinic acid

Urea Cycle & Hyperammonemia

Definition

- The function of urea cycle is to get rid of ammonia (Free NH_3 is highly toxic)

Biochemical Defect

- Five enzymes are involved in synthesis of urea:
  - Carbamyl phosphate synthetase (CPS)
  - Ornithine transcarbamylase (OTC)*
  - Argininosuccinate synthetase (AS): **Citrullinemia**
  - Argininosuccinate lyase (AL): **Argininosuccinic aciduria**
  - Arginase: **Hyperargininemia**
  - N-acetylglutamate synthetase *(activator of CPS)*

} **All are AR except OTC**

Epidemiology

- 1: 30.000 live births
- Most common genetic cause of hyperammonemia

Clinical Picture

Plasma NH_3 should be done in any ill infant witout evidence of infection

A. Neonatal period

- Normal at birth
- Poor feeding, vomiting, tachypnea
- Lethargy, coma, convulsions, ↑↑ ICT
- Hepatomegaly

B. Infants & older children

- Vomiting
- CNS: Ataxia, confusion, irritability (alternating with lethargy & coma)

Investigations

- ↑↑ NH_3 [Normal values: < 35 (children), < 100 (FT), < 150 µmol/L (Preterm)]
- ↓↓ BUN, ↑↑ ALT, AST
- ABG: Respiratory alkalosis, why?
- Metabolites
  - CPS, OTC & NAG deficiency: ↑↑ Glutamine & alanine and ↓↓ arginine & citrulline
  - OTC deficiency: ↑↑ urinary orotic acid
  - Oral carbamylglutamate improve patients with NAG synthetase (Not CPS)
  - AS, AL, arginase deficiency: ↑↑ citrulline, ↑↑ argininosuccinic acid, ↑↑ arginine

Inborn Errors of Metabolism causing Hyperammonemia:

- **Urea cycle defects:** 6 enzymes
- **Organic acidemia**
  - Methylmalonic acidemia
  - Propionic acidemia
  - Isovaleric acidemia
  - Multiple carboxylase deficiency
  - Beta-ketothiolase deficiency
  - 3-(OH)-3-methylglutaric aciduria
  - Glutaric aciduria type II
- **Lysinuric protein intolerance**
- **Hyperammonemia-hyperornithinemia-homocitrullinemia syndrome**
- **Transient hyperammonemia of the newborn**
- **Congenital hyperinsulinism with hyperammonemia**

Treatment of Acute Hyperammonemia

1. **Adequate Calories:**
   - IV fluid: electrolytes
   - Glucose 10%
   - Lipids: 1-2 g/Kg/day
2. **Protein restriction**
   - Protein: 0.25 g/Kg/day
   - Essential amino acids are preferred
3. **Enhancement of ammonia excretion**
   - ➢ Priming dose (250 mg/Kg to be added to 20 mL/Kg G10% over 1-2 hrs) of:
     - Na benzoate: Removes NH_3 in the form of hippuric acid
     - Phenylacetate: Removes NH_3 in the form of phenylacetylglutamine
     - Arginine: Except in arginase deficiency
   - ➢ Maintenance infusion (250 mg/Kg/day): Na benzoate, phenylacetate or arginine
4. **Dialysis**
   - If there is no significant decrease of NH_3
   - Hemodialysis is preferred
5. **Oral neomycin**
   - ↓↓ Intestinal production of NH_3
6. **Oral lactulose**
   - ↓↓ Intestinal absorption of NH_3

TTT of hyperammonemia should be rapid & aggressive (NH_3 is toxic)

Long-Term Treatment of Hyperammonemia

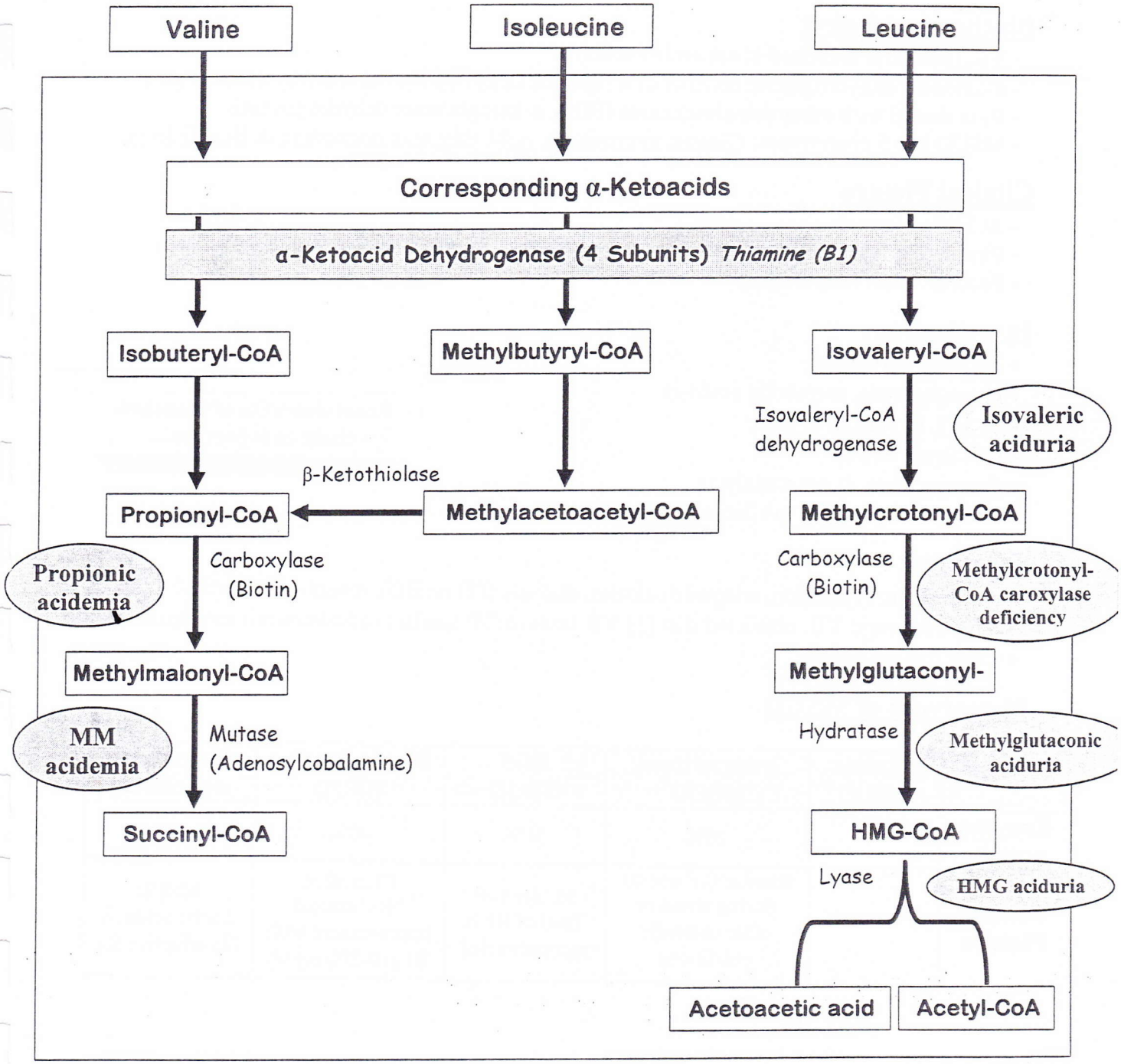
1. **Adequate Calories**
2. **Protein restriction**
   - Protein: 1-2 g/Kg/day
3. **Enhancement of ammonia excretion**
   - Na benzoate
   - Phenylacetate
   - Arginine
   - Citrulline: In OTC deficiency
4. **Carnitine supplementation**
5. **Avoid triggering factors:** Infections, fasting
6. **Avoid valproate,** why?

Transient Hyperammonemia of the newborn:

- **Blood ammonia in healthy nenates**
  - Blood ammonia is higher in neonates than adults
  - Level may be up to 100 µmol/L in FT neonates & 150 µmol/L in preterm neonates
  - Persists for few weeks
  - Asymptomatic
- **Severe Transient Hyperammonemia**
  - Unknown cause
  - Usually preterm with RDS
  - Level may be up to 4.000 µmol/L
  - Rx of hyperammonemia

Valine, Leucine & Isoleucine

(&Related Organic Acidemias)



Maple Syrup Urine Disease

Definition

- **AR** Deficiency of branched-chain α-ketoacid dehydrogenase (B_1 is cofactor)
- 1: 185.000

Biochemical Defect

- VIL (essential branched-chain amino acids)
- α-ketoacid dehydrogenase consists of 4 subunits ($E_{1\alpha}$, $E_{1\beta}$, E_2, E_3) coded by different genes
- E_3 is shared with other dehydrogenases (PDH, α-ketoglutarate dehydrogenase)
- MSUD has 5 phenotypes: Classic, intermittent, mild, thiamine responsive & E_3 deficiency

Clinical Picture

- At birth: Normal
- First week: Poor feeding, vomiting, lethargy, coma, seizures, hypertonia, opisthotonos
- Peculiar odor: Maple syrup

Investigations

- Neonatal screening
- Hypoglycemia, metabolic acidosis
- ↑↑ VIL in plasma & urine
- CT: Brain edema
- Enzyme assay & gene analysis
- Prenatal diagnosis is available (enzyme or gene analysis)

Renal clearance of branched-chain aa is poor, so…

Treatment

- Acute stage: Hydration, adequate calories, dialysis (PD or HD), mannitol, diuretics?
- After recovery: VIL restricted diet [↓↓ VIL leads to C/P similar to acrodermatitis enteropathica]
- Liver transplantation

Phenotypes of MSUD

	Classic MSUD	Intermittent MSUD	Mild MSUD	B_1-responsive MSUD	E_3 subunit deficiency
Enzyme activity		20%	30%	40%	
Clinical Picture		Similar C/P occurs during stress or other catabolic conditions	Milder C/P Trial of B1 is recommended	Clinical & biochemical improvement with B1 (10-200 mg/d)	MSUD Lactic acidosis No effective Rx

Propionic Acidemia

Definition

- **AR** (13q & 3q)
- Deficiency of **propionyl-CoA carboxylase** (**Biotin** is cofactor)
- 1: 5.000 (in KSA)

Biochemical Defect

- Propionyl-CoA carboxylase consists of 2 subunits (α & β) coded by 2 genes
- Cerebral atrophy & destruction of the BG (Metabolic stroke)

Clinical Picture

- At birth: Normal
- First few days: Poor feeding, vomiting, lethargy, coma, seizures, hyportonia, acidosis
- Survivors develop recurrences triggered by infection, constipation or high-protein diet
- Older children: MR, dystonia

Investigations

- Neonatal screening
- Metabolic acidosis (AG), ketosis, hypoglycemia, hyperammonemia (why?)
- **CBC:** Neutropenia, thrombocytopenia, anemia
- ↑↑ Glycine *(Ketotic hyperglycinemia)*
- ↑↑ Propinionic acid in plasma & urine
- CT: Metabolic stroke
- Enzyme assay & gene analysis
- Prenatal diagnosis is available (enzyme or gene analysis)

Treatment

A. Acute attack:

- Hydration
- Adequate calories with protein restriction
- TTT of hyperammonemia
- GIT sterilization: Oral neomycin or metronidazole
- Carnitine supplementation
- Oral biotin (10 mg/day)
- Dialysis: PD or HD

B. Long-term management:

- Adequate calories
- Protein restriction (Synthetic proteins deficient in propionic acid precursors are available?)
- Carnitine supplementation
- Chronic acidosis: alkali therapy
- Hyperammonemia?

Methylmalonic Acidemia

Definition

- **AR**
- Deficiency of **methylmalonyl-CoA mutase** or its coenzyme **adenosylcobalamin**
- 1: 48.000 (all forms)

Biochemical Defect

- ↓↓ Methylmalonyl-CoA mutase may be mut^0 *(absent activity)* or mut^- *(Decreased activity)*
- Seven defects in the intracellular metabolism of vitamin B12 (Cobalamin)
  - ➢ *cbl*A, *cbl*B, *cbl*D ⟹ Adenosylcobalamin (MMA)
  - ➢ *cbl*C, *cbl*F, cblD ⟹ Adenosyl- & Methylcobalamin (MA & Homocystinuria)
  - ➢ *cbl*E, *cbl*G, cblD ⟹ Methylcobalamin (Homocystinuria)
- C/P due to mut^0, mut^-, *cbl*A, *cbl*B, *cbl*D are similar
- Cerebral atrophy & destruction of the BG (Metabolic stroke)

Clinical Picture

- …
- ~~هههه~~…
- **Complications:** CRF, neurological, acute & recurrent pancreatitis

Investigations

- ↑↑ Methylmalonic acid in plasma & urine

Treatment

A. Acute attack:

- Vitamin B12 (1 mg/day)

B. Long-term management:

- Liver transplantation, renal transplantation

Isovaleric Acidemia

Definition

- **AR**
- Deficiency of **isovaleryl-CoA dehydrogenase**
- 1: 100.000

Clinical Picture

- Acute form: …
- Chronic intermittent form: …

Investigations

- Neonatal screening
- Metabolic acidosis (AG), ketosis, hyperglycemia, hyperammonemia
- **CBC:** Neutropenia, thrombocytopenia, anemia
- ↑↑ Isovaleric acid in plasma & urine
- Enzyme assay & gene analysis
- Prenatal diagnosis is available (enzyme or gene analysis)

Treatment

- Acute
- Long-term management

Hyperoxaluria & Oxalosis

Types

☒ **Primary hyperoxaluria:**
- Type I: Deficiency of alanine:Glyoxylate aminotransferase
- Type II: Deficiency of D-glycerate dehydrogenase

☒ **Secondary hyperoxaluria:**
- Pyridoxin deficiency
- High doses of vitamin C
- GIT cause: IBD, bowel resection
- Dietary: Spinach

Primary Hyperoxaluria Type I

Biochemical Defect

- Alanine:Glyoxylate aminotransferase is a peroxisomal enzyme
- The commonest mutation results in **mistargeting** of the enzyme to the mitochondria
- AR (2q)

Clinical Picture

- Renal stones & nephrocalcinosis: Renal colics, hematuria, renal impairment
- Arthritis, crystalline retinopathy

Investigations

- ↑↑ Urinary oxalate (also ↑↑ Glyoxylic & glycolic acid)
- Enzyme assay & gene analysis
- Prenatal diagnosis is available (enzyme or gene analysis)

Treatment

- Pyridoxine especially in patients with…
- Combined liver & kidney transplantation

Primary Hyperoxaluria Type II

Biochemical Defect

- Deficiency of D-glycerate dehydrogenase
- AR (9cen)

Clinical Picture

- Renal failure is less common

Investigations

- ↑↑ Urinary oxalate (Normal urinary glyoxylic & glycolic acid)

Treatment

- No effective TTT

Pyridoxine-Dependent Epilepsy

Etiology

a. **Antiquitin deficiency*:** Enzyme in the catabolic pathway of lysine
b. **Hypophosphatasia:** ALP is important for dephosphorylation of P5P

Clinical Picture Generalized intractable seizures (1st few hours)

Investigations EEG

Treatment Pyridoxine (5-100 mg/Kg): Dramatic response

Trial of pyridoxine is recommended in any infant with intractable seizures

Glutaric Aciduria Type I

Definition

- AR
- Deficiency of **Glutaryl CoA dehydrogenase enzyme** (Riboflavin is a cofactor)

Clinical Picture

- **Macrocephaly**, hypotonia, loss of head control, seizures, dystonia, acidosis

Investigations

- Neonatal screening
- Metabolic acidosis, ketosis, hypoglycemia, hyperammonemia
- ↑↑ Glutaric acid in urine, plasma & CSF
- Enzyme assay & gene analysis
- Prenatal diagnosis is available

Treatment

- Protein restriction
- Riboflavin, L-carnitine, Strychnine & phenytoin: some benefit

Canavan Disease

Etiology

- AR disease (More prevelent in Jews)
- Deficiency of aspartoacylase enzyme (↑↑ N-acetylaspatic acid in CNS, blood & urine)

Pathology Spongy degeneration of the white matter

Clinical Picture

- **Macrocephaly**, severe hypotonia followed by **hypertonia** & spasticity
- Joint stiffness & contractures
- Seizures, feeding difficulties, aspiration

DD: CP

Investigations

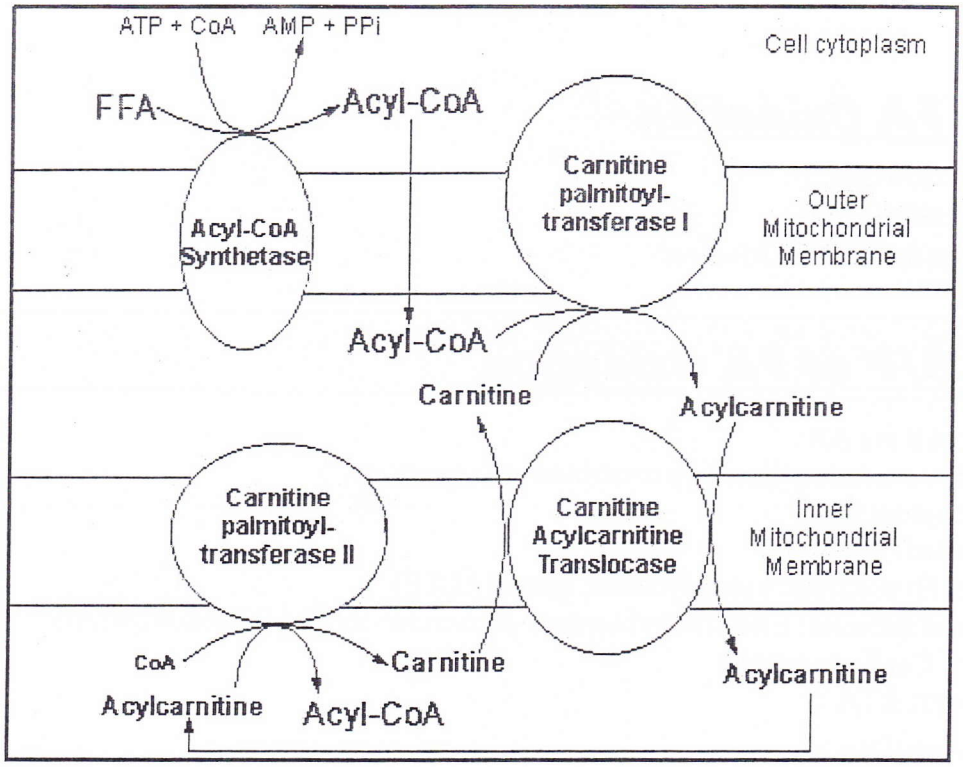
- ↑↑ Urinary & CSF N-acetylaspatic acid
- **Enzyme assay:** aspartoacylase enzyme
- **MRI:** White matter degeneration in the cerebral hemisperes
- **MRS:** High peak of N-acetylaspatic acid

Treatment (No specific Rx)

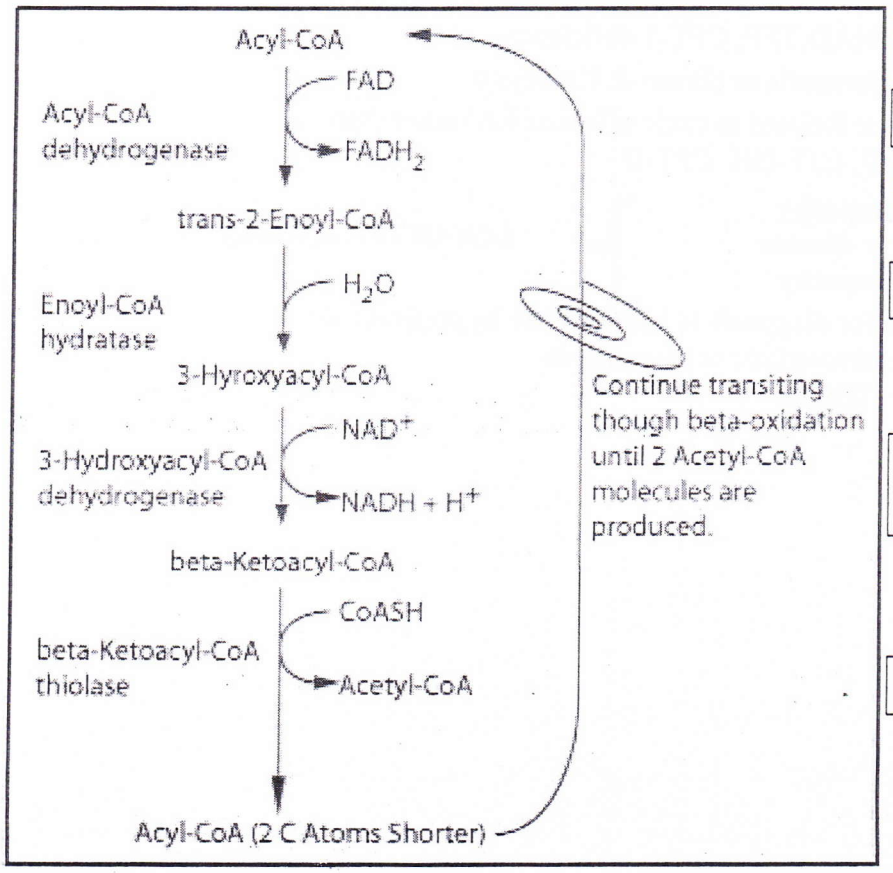
- Trials of aspartoacylase

Fatty Acid Oxidation

Carnitine Shuttle



Steps of β-FA oxidation



Acyl-CoA Dehydrogenase

???

Hydratase

Hydroxy Acyl-CoA Dehydrogenase

β-Ketothiolase

Energy?

Importance of FA Oxidation

- Starvation, Relation to Ketogenesis
- ↓↓ Caloric intake (……..)
- Exercise
- Heart?
- Brain?

Types of FA Oxidation

- ☒ **β-FA oxidation**
- ☒ **α-FA oxidation**
- ☒ **Peroxisomal FA oxidation**

General C/P of FA Oxidation

- Inheritance: **All** are AR
- Incidence: FA oxidation disorders combined are common
- May be asymptomatic?
- Organs affected?
  - ➢ **Liver:** Hypoketotic hypoglycemia, coma (ALTE)
  - ➢ **Skeletal muscles:** Exercise intolerance & exercise-induced rhabdomyolysis
  - ➢ **Heart:** Cardiomyopathy
  - ➢ **Kidneys:** RTA
- Other manifestations
  - ➢ **Fatty liver of pregnancy or preeclampsia with HELLP:**
    - When? Fetus , Mother
    - HELLP: Hemolysis, Elevated liver enzymes, Low platelet count
    - Mechanism: Related to toxic effect of FA rather than…
    - Types: LCHAD,TFP, CPT-1 deficiency
  - ➢ **Congenital malformations** (Brain & Kidneys)**:**
    - Mechanism: Related to toxic effect of FA rather than…
    - Types: ETF, ETF-DH, CPT-II
  - ➢ **Pigmented retinopathy**
  - ➢ **Progressive liver disease**
  - ➢ **Peripheral neuropathy**

  } *LCHAD/TFP deficiency*

- The only specific clue for diagnosis is **hypoketotic hypoglycemia**
- Neonatal screening: characteristic acylcarnitines
- DD: Reye syndrome, SIDS

Peroxisomal Disorders

Classification

A. Peroxisomal biogenesis defects:

- Failure to import one or more proteins into the peroxisomes
- Peroxisomes: Absent or decreased
- Abnormalities of multiple peroxisomal functions are present
- Disorders:
  - ☒ Zellweger syndrome (ZS)
  - ☒ Neonatal adrenoleukodystrophy (NALD)
  - ☒ Infantile Refsum disease (IRD)

  } *Zellweger spectrum disorders*

  - ☒ Rhizomelic chondrodysplasia punctata (RCDP)

B. Single enzyme defect

- Defect in the function of a single peroxisomal enzyme
- Peroxisomes: Normal number & structure
- Abnormality of single peroxisomal function
- Disorders:
  - ☒ X-linked adrenoleukodystrophy
  - ☒ Acyl CoA oxidase deficiency
  - ☒ Peroxisomal thiolase deficiency
  - ☒ Classic Refsum disease
  - ☒ Mevalonic aciduria
  - ☒ Glutaric aciduria type III
  - ☒ Hyperoxaluria type I
  - ☒ Acatalasemia

Epidemiology

- 1: 50.000 live births
- X-ALD is the commonest (1:20.000)
- All are AR except…
- Antenatal diagnosis is available

Pathology

- PBD: Absent or decreased peroxisomes with peroxisome "Ghosts"
- Multisystem affection:
  a. **Nervous system:** Defect in neuronal migration, MR, hypotonia
  b. **Liver:** Hepatomegaly, cirrhosis
  c. **Skeletal:** Chondrodysplasia puctata
  d. **Eye:** Cataract, glaucoma, retinopathy
  e. **Herat:** CHD
  f. **Dysmorphic features**

Mechanism?

Refsum Neuropathy

Etiology AR[10] (Phytanoyl CoA oxidase)

Pathogenesis Failure of α-FA oxidation ⟶ accumulation of phytanic acid

C/P Polyneuropathy, ataxia, retinitis pigmentosa, blindness, deafness, icthyosis (scaly skin)

Investigations ↑↑ Serum phytanic acid, ↓↓ NCV

Treatment ↓↓ Dietary phytanic acid (nuts, coffee)
Plasmapheresis

Zellweger Syndrome

DD?

Genetics

- AR; most common cause are mutation in **PEX1** & **PEX6**

Clinical Picture

- Dysmorphic facies: high forehead, hypoplastic supraorbital ridges, epicanthal folds, midfacial hypoplasia, large fontanel
- Ocular: Cataract, glaucoma, corneal clouding, brush-field spots, nystagmus, optic nerve hypoplasia, pigmentary retinopathy
- Hypotonia, seizures, psychomotor retardation, sensorineural deafness
- Hepatomegaly, cholestasis, cirrhosis
- Renal cysts

Neonatal Adrenoleukodystrophy

Genetics

- AR, mutation in PEX genes (e.g., PEX1…)

Clinical Picture

- Dysmorphic facies: Few or absent
- Ocular: Pigmentary retinopathy
- Hypotonia, seizures, psychomotor retardation, sensorineural deafness
- Hepatomegaly, cholestasis,cirrhosis
- Adrenal function is usually impaired

Infantile Refsum Disease

Genetics

- AR, mutation in PEX genes (e.g., PEX1…)

Clinical Picture

- Dysmorphic facies: Few or absent
- Ataxia (broad based gait)
- Ocular: Pigmentary retinopathy
- Hypotonia, seizures, **psychomotor retardation**, sensorineural deafness
- Hepatomegaly, cholestasis, cirrhosis

Rhizomelic chondrodysplasia Punctata

Genetics

- AR, mutation of PEX7 (receptor for PTS2)

Clinical Picture

- Disproportonate short stature (Rhizomelic =)
- Dysmorphic facies: Depressed nasal bridge, hypertelorism
- Cataract, psychomotor retardation, icthyosis, quadriplegia (why?)

Investigations

- Radiology: epiphyseal stippling, vertebral body clefts

Approach to Diagnosis of Peroxisomal Disorders

A. Level 1: Confirm the diagnosis of peroxisomal disorder

- VLCFA: ↑↑ (Normal in RCDP)
- Phytanic acid
- Pipecolic acid
- RBC plasmalogen
- Bile acids

B. Level 2: Precise nature of the peroxisomal disorder

Disorder	VLCFA	RBC plasmalogen	Pipecolic acid	Phytanic acid	Bile acid
ZS, NALD, IRD	↑↑	↓↓	↑↑	↑↑	↑↑
RCDP	N	↓↓	N	↑↑	N
Classic Refsum	N	N	N	↑↑	N
X-ALD	↑↑	N	N	N	N
Bifunctional enzyme	↑↑	N	N	↑↑	↑↑

C. Level 3: Molecular defect of peroxisomal disorder: PEX genes

Treatment

- Classic Refsum disease:
- Supportive TTT
- Oral docosahexaenoic acid

Adrenoleukodystrophy

Definition

- Peroxisomal disorder characterized by accumulation of VLCFA in CNS & adrenal cortex
- Neonatal ALD & XL-ALD

XL-Adrenoleukodystrophy

Etiology

- Defect in peroxisomal degradation of **VLCFA** (Due to ↓↓ **lignoceroyl CoA ligase**)
- Accumulation of VLCFA in CNS & adrenal cortex
- Not rare; 1:20.000 ♂

Pathogenesis

- Accumulation of VLCFA ⟶ adrenal dysfunction
- CNS: Inflammation (Demyelination); mostly in the parieto-occcipital area

Clinical Picture "Five phenotypes are recognized"

A) Childhood cerebral form
- Onset: 4-8 years
- Hyperactivity (DD: ADHD), academic deterioration
- Impaired auditory discrimination, visual disturbane, ataxia
- Seizures, spastic quadriparesis
- Bulbar manifestations
- ↑↑ ICT, unilateral mass lesion
- **Adrenal insufficiency:** Usually follows but may precedes neurologic manifestations

B) Adolescent ALD: Delayed onset & less progressive course

C) Adrenomyeloneuropathy
- Affection of spinal cord & peripheral nerves in adolescents & adults
- Progressive paraparesis, urinary incontinence, impotance

D) Addison only: 25% of Addison patients have biochemical defects of ALD, so…

E) Asymptomatic ALD

NB: 50% of heterozygous ♀ may have milder adrenomyeloneuropathy

Investigations

- ↑↑ **VLCFA** in plasma, RBC, fibroblasts
- **CT, MRI:** Typically symmetric periventricular in the posterior parietal & occipital lobes
  Unilateral lesion with mass effect (DD: Tumor) may occur
- **Adrenal** function tests: ACTH, cortisol after ACTH stimulation

Treatment

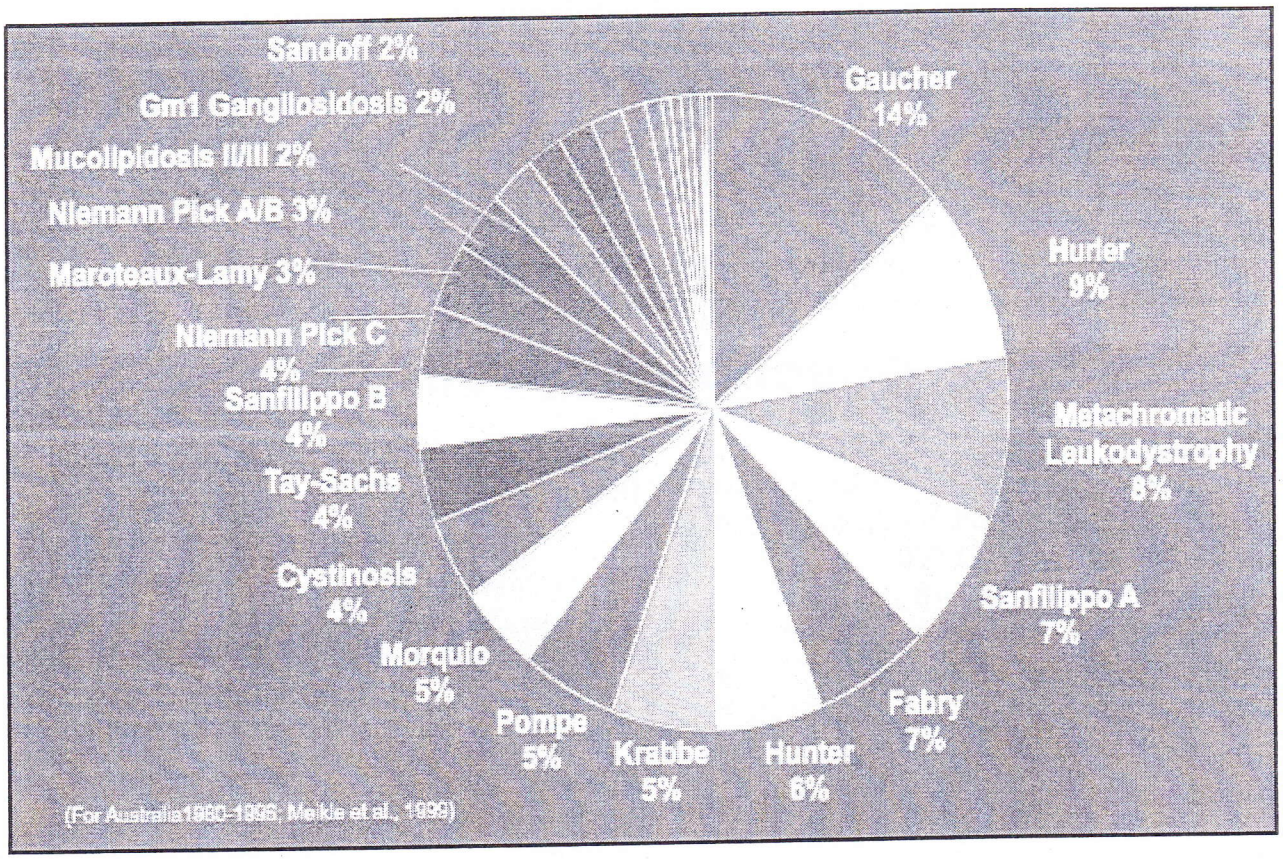
- **BMT:** Considered in neurologically asymptomatic or mildly affected patients
- **Lorenzo's oil:** ↓↓ VLCFA synthesis
- **Adrenal replacement**

Prevention & Genetic counseling

- **Family screening:** VLCFA (allows early diagnosis of presymptomatic individuals, why?)
- **Antenatal diagnosis:** VLCFA (amniocytes or CVS) or molecular testing
- **Addison males**

DD ADHD, other leukodystrophies, MS, brain tumors, epilespsy, Addison

Lysosomal Disorders



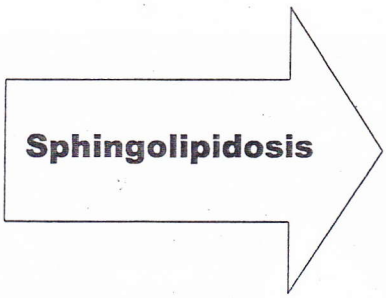
Lysosomal Storage Diseases:

1. Sphingolipidosis (6 + 4)
2. MPS
3. Mucolipidosis
4. Fucosidosis
5. NCL
6. Sialidosis

Sphingolipidosis

Definition

- Group of diseases characterized by accumulation of sphingolipids
- Sphingolipids: Sphingosine-containing lipids *(Cerebrosides, gangliosides)*
- Sphingosine is an amino alcohol



Sphingolipidosis:
1. GM 1 Gangliosidosis
2. GM 2 Gangliosidosis
3. Krabbe disease (KD)
4. Metachromatic LD
5. Gaucher
6. Niemann-Pick

Other Sphingolipidosis:
1. Fabry
2. Farber
3. Wolman
4. Multiple sulfatase deficiency

Gaucher Disease

Etiology

- Glucocerebrosidase (β-Glucosidase) deficiency (AR^1)
- **Four** mutations account for the majority of cases
- Incidence in Jews = 1/1.000
- Carrier rate in Jews = 1/18

Gaucher should be considered in the DD of any child with unexplained organomegaly

Clinical Picture

	Type 1* (99%)	Type 2	Type 3
Other Names	Adult type Non-Neuropathic	Infantile Acute neuropathic	Juvenile Subacute neuropathic
Onset	Variable	Infancy	Early childhood > 2yrs
C/P	▪ HSM (S > L) ▪ Anemia ▪ Thrombocytopenia ▪ Bruises ▪ Bony pains ▪ Pathologic fractures ▪ Normal mentality (?? Chronic disease)	▪ HSM ▪ Hypertonia ▪ Head retraction ▪ Laryngospasm ▪ Stridor ▪ Squint ▪ Cranial nerve… ▪ Rapid **neurologic**…MR ▪ Death in the 1st 2 yrs	▪ HSM ▪ **Neurologic** (Less severe) ▪ MR ▪ Ataxia ▪ Myoclonic epilepsy ▪ Gaze palsy ▪ Death by age of 10-15 y

Investigations

- X-rays: Lytic lesions, Erlenmeyer flask deformity (Distal femur)
- BM examination: Gaucher cells (Positive PAS stain)
- Enzyme assay: Leukocytes or fibroblast
- Carrier detection: Molecular testing (4)
- Antenatal diagnosis is available

Not Pathognomonic

Treatment

- Enzyme replacement: Cerezyme (IV infusion every other week): **No** effect on CNS
- BMT
- Gene therapy

Niemann-Pick Disease

Etiology

- Type A & B: Sphingomyelinase deficiency (AR^{11})
- Type C: Defective cholesterol transport (with 2ry sphingomyelinase deficiency)

Clinical Picture

	Type A	Type B	Type C
Other Names	Acute infantile	Non-Neuropathic	Neuropathic
Onset	1st few months of life	Infancy or childhood	Early childhood > 2yrs
C/P	▪ HSM (**L** > S) ▪ FTT, feeding difficulties ▪ Neurological…MR ▪ Cherry-red spots (50%) ▪ Spasticity ▪ Death in the 1st 3 yrs	▪ HSM ▪ Pulmonary involvement ▪ Dyspnea, pneumonia ▪ **No neurological…** ▪ Normal mentality ▪ Hypersplenism	▪ Ataxia ▪ Slowly progressive neurologic course ▪ Gaze palsy ▪ HSM *(Less severe)*

Investigations

- BM examination: Foam cells (NP cells)
- Enzyme assay (Leukocytes or fibroblasts)
- CXR (Type B): Reticular or nodular infiltration
- Antenatal diagnosis is available

Treatment

- Supportive
- Liver transplantation
- Enzyme therapy in type B (Phase I trial)

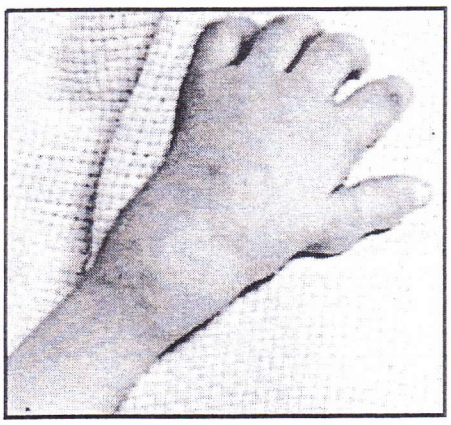
Farber Disease

Etiology

- Ceramidase deficiency (AR)
- Accummulation of ceramide in various tissues, especially the joints

Clinical Picture

- Onset: 1st year of life
- Joint: Painful swelling & nodules
- Vocal cord nodules: Hoarseness of voice



Investigations

- Enzyme assay (Leukocytes or fibroblasts)
- Antenatal diagnosis & carrier detection is available

Treatment

- Supportive

Fabry Disease

(See before)

Gangliosidosis

Definition Accumulation of gangliosides (Glycosphingolipids)

GM_1 Gangliosidosis

Etiology

- β-Galactosidase deficiency (AR^3) ⟶ Accumulation of GM_1 gangliosides (CNS & visceral)

Clinical Picture

	Infantile*	Juvenile	Adult
Other Names	**Type 1**	**Type 2**	**Type 3**
Onset	Birth	1 year	Adult
C/P	▪ Poor feeding ▪ HSM ▪ Global developmental delay ▪ Seizures ▪ Spasticity ▪ Hurler-like… ▪ Dysostosis multiplex ▪ Blindness & Deafness ▪ Cherry-red spots ▪ Angiokeratoma ▪ Death in the 1st 3 yrs	▪ Ataxia ▪ Mental retardation ▪ Seizures ▪ Spasticity ▪ Blindness ▪ **No** HSM ▪ **No** Hurler-like… ▪ Death in the 1st 10 yrs	▪ Ataxia ▪ Spasticity ▪ Dysarthria ▪ ↓↓ Cognitive function

GM_2 Gangliosidosis

Etiology

- **Tay-Sachs:** AR^{15} **Sandhhoff:** AR^5
- Carrier rate of Tay-Sachs in Jews = 1/25

Clinical Picture

	Tay-Sachs	Sandhoff	Juvenile & Adult
Genetics	**HEXA gene** (Chromosome 15)	**HEXB gene** (Chromosome 5)	-
Defect	Hexosaminidase A	Hexosaminidase A & B	
Onset	5-6 months		Childhood-adult
C/P	▪ Marked startle reaction (= **Hyperacusis**) ▪ Regression ▪ No HSM ▪ Seizures ▪ Early hypotonia ⟶ Spasticity ▪ Blindness & Deafness ▪ Macrocephaly ▪ Cherry-red spots ▪ Death in the 1st 3-5 yrs ▪ **Splenomegaly** (HSM) **in Sandhoff**		▪ Ataxia ▪ Spasticity ▪ Dysarthria

Investigations

- Enzyme assay: Leukocytes or fibroblast
- Antenatal diagnosis & carrier detection is available (Enzyme activity)

Treatment Supportive

Macroglossia:
1. MPS
2. Gangliosidosis
3. Hypothyroidism
4. BW syndrome
5. Fucosidosis

Krabbe Disease

(Globoid Cell Leukodystrophy)

Etiology

- Galactocerebroside β-Galactosidase deficiency (AR)
- Accummulation of Galactocerebroside ⟶ Myelin destruction (Vicious circle)

Clinical Picture

- Onset: 1st months of life
- Irritability, crying, spasticity, opisthotonos, Seizures
- Neuropathy, absent deep reflexes

(DD: Colic, milk allergy…)

Investigations

- Enzyme assay (Leukocytes or fibroblasts)
- Antenatal diagnosis & carrier detection is available

Treatment

- Stem cell transplantation may improve the outcome if given very early

Metachromatic Leukodystrphy

Etiology

- Arylsulfatase deficiency (AR^{22})
- Accummulation of cerebroside sulfate ⟶ Myelin destruction *(CNS & peripheral nerves)*
- Classified into: Late infantile, juvenile & adult types

Clinical Picture

- Onset: 1-2 year
- Regression (Loss of ability to walk…)
- Hypotonia, Seizures
- Neuropathy, absent deep reflexes

Investigations

- ↓↓ NCV, ↑↑ CSF proteins
- Enzyme assay (Leukocytes or fibroblasts)
- Antenatal diagnosis & carrier detection is available

Treatment

- Stem cell transplantation may improve the outcome if given very early

Wolman Disease

Etiology Acid lipase deficiency (AR) ⟶ Accumulation of cholesterol esters

Clinical Picture FTT + Steatorrhea + HSM + Calcification of the adrenal glands

Neuronal Ceroid Lipofuscinosis

Definition

- Lysosomal storage disorder
- Intracellular accumulation of fluorescent lipopigments, ceroid & lipofuscin
- NCL is characterized by visual loss, seizures, motor deterioration & early death
- Traditionally classified into: Infantile, Late infantile & juvenile types

Mucopolysaccharidosis

Biochemistry

☒ **Monosaccharide:** Glucose, Galactose, Fructose
☒ **Disaccharide:** Maltose, Lactose, Sucrose
☒ **Polysaccharide:**
- Homo-: Glycogen, Starch, Inulin, Agar
- Hetero-: Glycosaminoglycans (= MPS)

GAG:
- Chondroitin sulfate
- Dermatan sulfate
- Keratan sulfate

} *(CT)*

- Heparan sulfate *(CNS)*
- Hyaluronic acid

Definition

- Lysosomal inherited disorders caused by incomplete degradation & storage of GAG
- **MPS-III** is the most common followed by MPS-I & II
- Incidence = 4: 100.000

Mode of Inheritance

All are AR except Hunter (Type II)

Clinical Picture

- Normal at birth, Why???
- Progressive course
- Nasal discharge
- All have corneal Clouding except…
- Deafness in Type…
- Hernia (Recurrent)
- Main organs: Bones, Cartilages, Joints, Tendons, CT, Skin, CNS

Classification

With…	Without…
Hurler syndrome (Type I-H)	Morquio syndrome (Type IV)
Hunter syndrome (Type II)	Scheie syndrome (Type V = Type I-S)
Sanfilippo syndrome (Type III)	Maroteaux-Lamy syndrome (Type VI)

- **Sly disease (Type VII):** Wide range of clinical involvement (Fetal hydrops- delayed onset)
- **Type IX:** Periarticular soft tissue masses & short stature

Dysostosis Multiplex

- Radiological changes
- Features
  - ➢ Skull: Macrocephaly, Dolicocephaly, J-shaped sella turcica
  - ➢ Clavicles: Thickening of the medial 1/3
  - ➢ Ribs: Spatulated (oar-shaped)
  - ➢ Vertebrae: Ovoid with anterior beaking
  - ➢ Iliac bones: Flaring
  - ➢ Radius & Ulna: Abnormal with V-shaped articulation
  - ➢ Metacarpals: Pointed proximally (5^{th}*)
  - ➢ Phalanges: Pointed distally (bullet-shaped)

Diagnosis

☒ **Clinical**
☒ **Radiological:** Dysostosis multiplex
☒ **Urinary GAG**
☒ **Enzyme assay** (Serum, WBC, Fibroblasts): α-L-Iduronidase in MPS-I-H

MPS-I

Hurler Syndrome

1. **At birth:** Normal (Diagnosis is usually made between 6-24 months)
2. **1st year:**
   - Persistent nasal discharge & obstruction
   - MR, HSM, Kyphosis
3. After the 1st year
   - Nasal discharge, MR, HSM, Kyphosis
   - Obstructive airway disease (OSA)
   - Coarse facies: Coarse hair, large head, hypertelorism, depressed nasal bridge, low-set ears, macroglossia, thick lips
   - Cardiac: Cardiomyopathy, coronary stenosis, valvular affection (AR, MR)
   - Hydrocephalus (Communicating)
   - Skeletal: Joint stiffness, claw hand, kyphosis, hernia, X-rays (Dysostosis multiplex)

α-L-Iduronidase

Most severe

Scheie Syndrome

1. Previously called Type V
2. C/P appears after the age of 5 years
3. Corneal clouding
4. Claw hand
5. Carpal tunnel syndrome
6. Aortic regurgitation
7. Normal mentality

Mildest

5

MPS-II Hunter Syndrome

1. As Hurler but milder
2. XLR, No Corneal clouding
3. Deafness
4. Hydrocephalus
5. Skin papules

Iduronate-2- sulfatase

XLR الوحيد
No corneal clouding الوحيد

Sanfilippo Syndrome

1. Rapid neurological deterioration
2. Severe MR
3. Mild dysmorphism

Neurological

Morquio Syndrome

1. Short stature
2. Skeletal: Kyphosis, flat feet, genu valgum, platyspondyly
3. HSM, corneal clouding…
4. Small separated teeth, broad mouth
5. Atlant-oaxial instability

Skeletal

β-Galactosidase

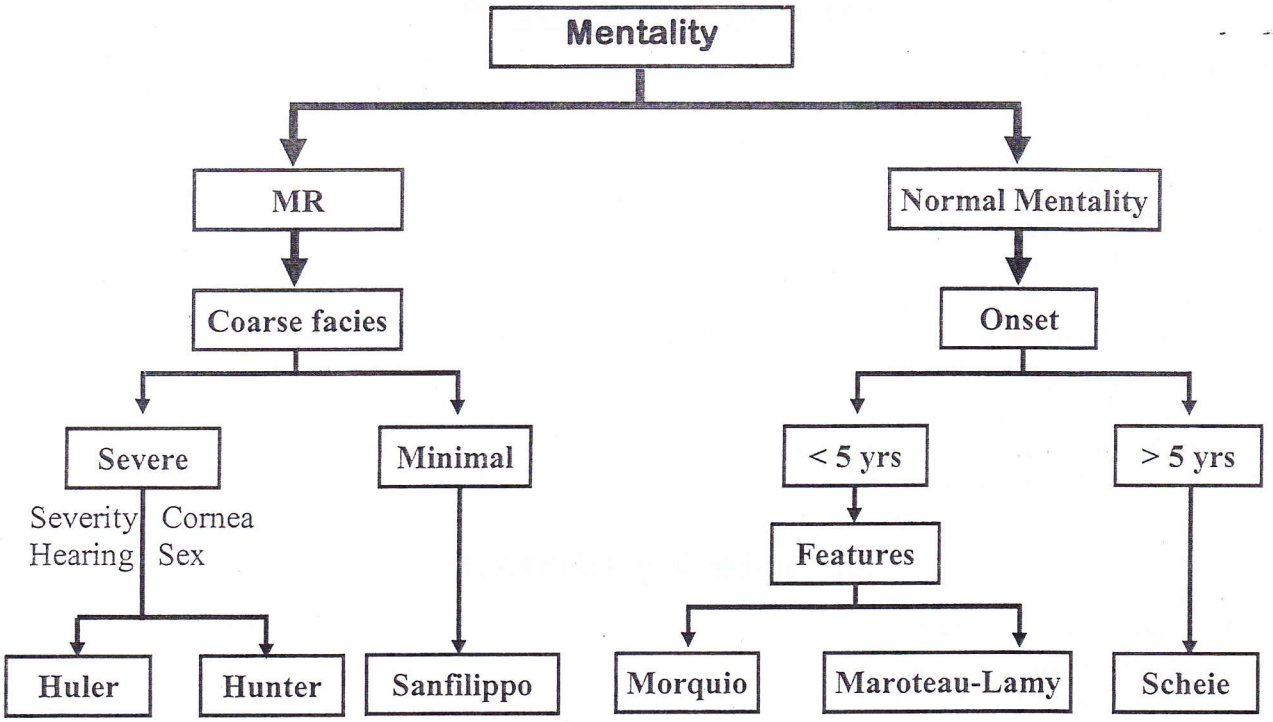
Maroteaux-Lamy Syndrome

1. As Hurler but delayed onset & slower course
2. Normal mentality

Arylsulfatase B

No MR

Clinical Approach to a case of MPS



Regular Assessment

- ☒ General history & examination
- ☒ Audiometry
- ☒ Visual acuity, corneal & retinal examination
- ☒ FVC & sleep study
- ☒ ECG, Echo

Treatment

- ☒ **HSCT:** MPS I, II, VI
- ☒ **Enzyme replacement: HSCT:** MPS I, II, VI
- ☒ **Combined**
- ☒ **Multidisciplinary care**

Hurler-like Diseases:

1. GM 1 Gangliosidosis
2. Mucolipidosis
3. Fucosidosis
4. Sialidosis typeII
5. Mannosidosis

Glycogen Storage Diseases

Types

Disease	Enzyme Defect	Clinical Picture
Type Ia (Von Gierke)	G-6-Phosphatase	Doll face Marked Hepatomegaly Fasting hypoglycemia (Seizures) Hypercholesterolemia Lactic acidosis ↑↑ Uric acid
Type Ib	G-6-Phosphate Translocase	GSD I + Neutropenia
Type II (Pompe)	Acid maltase	Hepatomegaly Myopathy Cardiomyopathy
Type III (Cori)	Debranching	Hepatomegaly Hypoglycemia Myopathy
Type IV (Andersen)	Brancher	HSM Liver cirrhosis LCF Ascites
Type V (Mc Ardle)	Muscle Phosphorylase	Exercise intolerance Muscle cramps Easy fatigability
Type VI (Hers)	Liver Phosphorylase	
Type VII (Tauri)	PFK	V + Hemolytic anemia
~~**Type VIII**~~		??Ataxia
Type IX	Phosphoglycerate Kinase	
~~**Type X**~~		
Type XI (Fanconi-Bickel)	Glucose Transporter II	FTT + Fanconi + Hepatomegaly
Type 0	Glycogen synthase	Fasting hypoglycemia (Seizures) Prolonged hyperglycemia (after meals)

Diagnosis

- Biochemical
- Liver biopsy
- Enzyme assay (Liver)

Treatment

- Avoid…
- Enzyme?
- Liver transplantation

Hepatic	Muscle	Mixed

Galactosemia

Etiology

1. Galactose 1-P-uridyltransferase deficiency** (Classic Galactosemia)
2. Galactokinase deficiency (Only cataract)
3. Epimerase deficiency

Clinical Picture

- Jaundice (Cholestasis)
- Hepatomegaly, splenomegaly, ascites
- Hypoglycemia, convulsions, lethargy
- FTT, vomiting
- Cataract
- E.coli sepsis

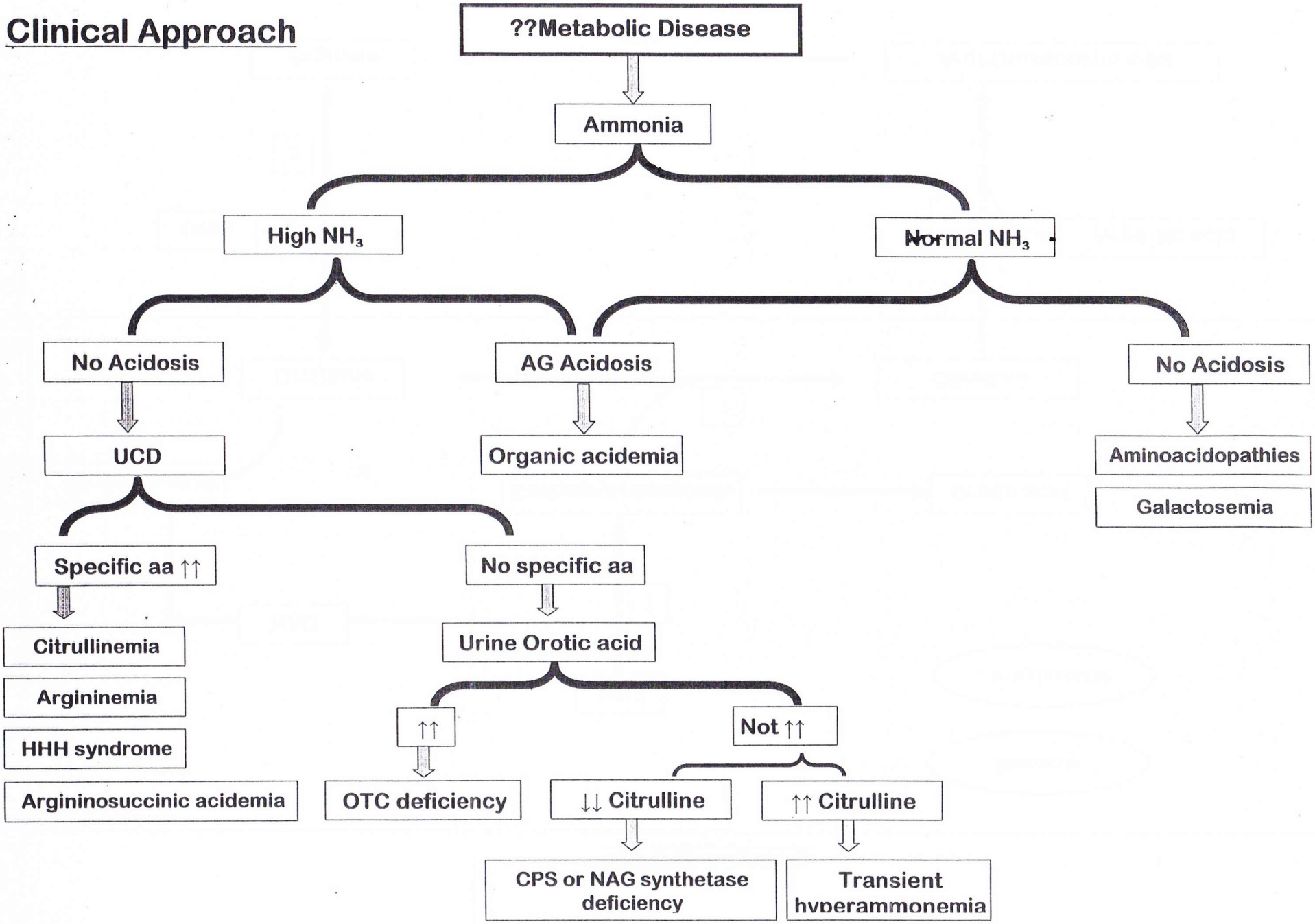
Diagnosis

- Reducing substances in urine (When?)
- Enzyme assay

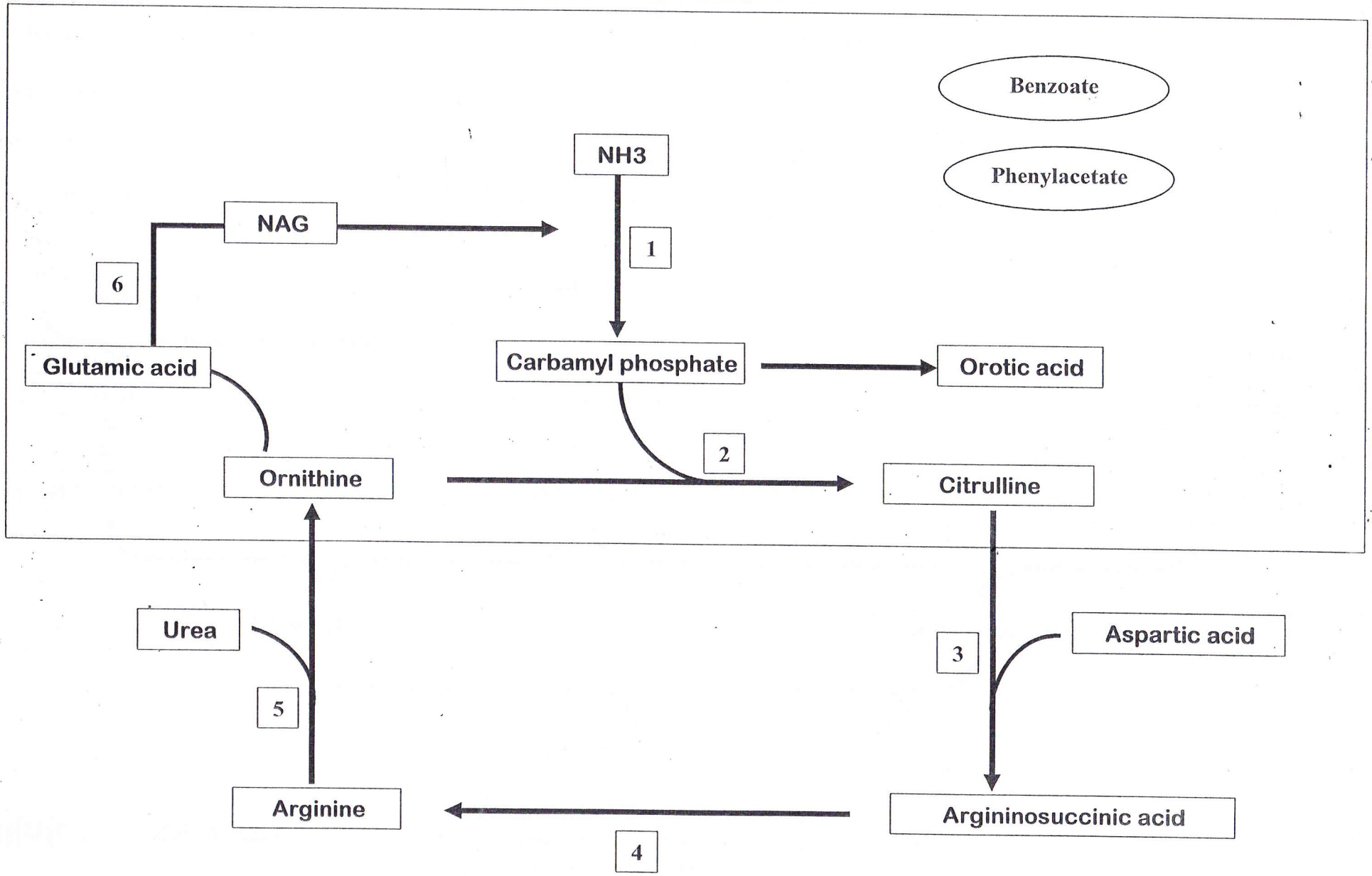
Treatment

Hereditary fructose intolerance

Clinical Approach



Urea Cycle


Benzoate
Phenylacetate
NH3
NAG
1
6
Glutamic acid
Carbamyl phosphate
Orotic acid
2
Ornithine
Citrulline
Urea
3
Aspartic acid
5
Arginine
Argininosuccinic acid
4